Low troponin I concentrations and clinical decision making

October 2009

Per Venge
MD, PhD
Professor
Department of Medical Sciences
University of Uppsala

Troponin values above the 99th percentile and increasing/falling values found by serial testing in addition to signs and symptoms of myocardial ischemia means AMI.

Low troponin values, near or below the 99th percentile, can be used for prognosis. Highest hazard ratios were found when using the 90th percentile, which suggests that lower cut-offs offer some clinical advantages.

When assays have detection limits identical to or above the 99th percentile, it means that we do not know the actual 99th percentile and that is a problem. We cannot be sure that we detect all AMI patients and these assays are also less useful for prediction.

Cardiac troponins as diagnostic markers

Cardiac troponins are the preferred markers of myocardial injury and are used for the diagnosis of acute myocardial infarction (AMI), but also for prediction of outcome of patients suffering from the acute coronary syndrome (ACS).

In the use of cardiac troponins as diagnostic markers we are guided by the recommendations given in the consensus documents published in 2000 and subsequently revised in 2007 [1]. These guidelines recommend that the diagnosis of AMI, in addition to symptoms and signs of myocardial ischemia, should include elevated levels of cardiac troponins above the 99th percentile of healthy references (99th percentile URL).

Elevated levels of cardiac troponins, however, are frequent findings of many other conditions than AMI, and the addition was therefore made to the recommendations that cardiac troponins should show a rise and/or fall in conjunction to the acute episode.

A requirement to the cardiac troponin assays was that they should be able to measure levels of cardiac troponins at the 99th percentile with acceptable imprecision, which was set to ≤10 % CV (coefficient of variation). This requirement, however, was at the time met by very few assays and is still a major challenge to most current commercial assays.

The use of cardiac troponins for outcome prediction has grown increasingly important and the common view today is that any elevation of cardiac troponins, whatever the cause, signifies a pathological process in the myocardium and is associated with an unfavorable outcome such as death or myocardial infarction.

In this regard two questions remain to be answered:

- What is an elevated troponin level?
- How do we define the 99th percentile URL?

What is an elevated troponin level - and how do we define the 99th percentile URL?

Recent assay developments have allowed us to answer these questions, since these assays measure cardiac troponin I well below the 99th percentile. As to the second question, it became apparent that the 99th percentile of the upper reference limit is highly dependent on the age distribution of the reference population with lower levels found in younger subjects [2].

Should we therefore regard the levels found in the younger population <60 years of age as the truly normal levels? This latter view was supported by the fact that seemingly healthy 70-year-old men with levels above the 99th percentile for the reference population <60 years of age, but below the 99th percentile for the entire reference population, experienced a significantly higher rate of death during a 10-year follow-up period than those having levels below the 99th percentile for the younger population, i.e. the "true" 99th percentile URL [3].

In recent reports we have extended these investigations [4]. Thus, in a community-based study (PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors) of about 1000 apparently healthy 70-year-old men and women we established the 99th percentiles for the TnI assay in the entire cohort to be 0.044 µg/L (i.e. close to the 99th percentile of 0.04 µg/L established previously for the assay used), whereas the 99th percentile was lowered to 0.028 µg/L if subjects with any sign of cardiovascular disease such as elevated levels of natriuretic peptides were excluded, i.e. the healthiest part of the population.

This healthy population included 520 subjects, 52 % women and 48 % men. For the sake of investigation we also defined the 97.5th, 90th and 75th percentiles and found them to be 0.022, 0.013 and 0.009 µg/L, respectively. The imprecision of the assay was ≤10 % CV at 0.014 µg/L and ≤20 % at 0.008 µg/L. At all cut-offs the levels were more often elevated in men.

These different cut-offs were then applied to the results of the FRISC II population, which is a population of NSTEMI myocardial infarction and unstable angina. Altogether cardiac troponin I results at 6 months after randomization were available in 952 patients. The prediction of 5-year mortality applying these different cut-offs was then calculated.

The results showed that the hazard ratio was not increased when the 99th percentile cut-offs were applied, whereas the hazard ratios increased substantially by the application of lower cut-offs. The highest hazard ratios (3.2, 1.9-5.1 95 % CI) were found with the 90th percentile cut-offs and independent of sex.

These data clearly suggest that applications of lower cut-offs offer some clinical advantages and that assays with lower sensitivities might not be optimal for clinical purposes.

It should be emphasized that the clinical application of highly sensitive cardiac troponin assays and the application of lower 99th percentiles reflecting the "true" 99th percentiles of healthy subjects will result in

Cut-off	Sensitivity	Specificity	Negative predictive value	Positive predictive value
90th percentile	47.9 %	76.7 %	94.8 %	14.2 %
99th percentile	9.9 %	92.3 %	92.7 %	9.3 %

TABLE 1: Predicting 5-year mortality - sensitivity, specificity and predictive values

many more discoveries of patients with elevated cardiac troponin levels and who do not suffer from AMI.

For this reason serial measurements of patients with suspected AMI should be performed in order to detect significant changes in the levels. We should also adhere strictly to the complimentary criteria of defining AMI [5].

Elevated levels of cardiac troponins are signs of myocardial injury and/or dysfunction and are seen in many other conditions, not least in patients with heart failure [6-8]. In many of these cases the slightly elevated levels are consequences of chronic processes, but as has been emphasized above, any such elevation of troponins is a sign of poor prognosis.

At the IFCC website (www.ifcc.org) the Committee for Standardisation of Markers of Cardiac Damage offers a table of analytical characteristics of most commercial cardiac troponin I and T assays (latest version October 2008). The list is based on the characteristics stated by the manufacturers:

- LoD (limit of detection)
- 99th percentile
- 10 % CV
- Risk stratification (per FDA clearance)
- Epitopes recognized
- Detection antibody tag

Results

When reading the list, however, it should be remembered that the definitions of the characteristics are not uniform. For some manufacturers slight changes have also been made to the assays with improvement of imprecisions, but which for various reasons are not claimed by the manufacturers. In assays in which the detection limits are identical to or above the 99th percentiles we do not know the actual 99th percentile. With the use of such assays we cannot be sure that we detect all patients with AMI and, moreover, they are less useful for prediction.

The major lessons learnt from our studies are the inherent difficulties in defining clinically useful decision limits for cardiac troponins, since the definitions of cut-offs are so dependent on the populations on which these are based. By the application of the novel sensitive troponin assays we also see that any elevation of cardiac troponins is predictive of adverse outcome, whether the patient is diagnosed with cardiovascular disease or not.

In the clinical application of cardiac troponins it is important to distinguish between diagnosis and prediction. The application of these highly sensitive cardiac troponin assays will inevitably make the distinction between what is normal and what is abnormal less clear, but they should constitute powerful tools in the future for primary and secondary prevention of myocardial disease.

References

1. Thygesen K, Alpert JS, White HD, Jaffe AS, Apple FS, Galvani M, *et al.* Universal definition of myocardial infarction. Circulation 2007 Nov 27; 116(22): 2634-53.

2. Venge P, Johnston N, Lagerqvist B, Wallentin L, Lindahl B. Clinical and analytical performance of the liaison cardiac troponin I assay in unstable coronary artery disease, and the impact of age on the definition of reference limits. A FRISC-II substudy. Clin Chem 2003 Jun; 49(6 Pt 1): 880-86.

3. Zethelius B, Johnston N, Venge P. Troponin I as a predictor of coronary heart disease and mortality in 70-year-old men: a community-based cohort study. Circulation 2006 Feb 28; 113(8): 1071-78.

4. Eggers KM, Jaffe AS, Lind L, Venge P, Lindahl B. Value of cardiac troponin I cutoff concentrations below the 99th percentile for clinical decision-making. Clin Chem 2009 Jan; 55(1): 85-92.

5. Eggers KM, Lind L, Venge P, Lindahl B. Will the universal definition of myocardial infarction criteria result in an overdiagnosis of myocardial infarction? Am J Cardiol 2009 Mar 1; 103(5): 588-91.

6. Eggers KM, Lindahl B, Venge P, Lind L. B-type natriuretic peptides and their relation to cardiovascular structure and function in a population-based sample of subjects aged 70 years. Am J Cardiol 2009 Apr 1; 103(7): 1032-38.

7. Eggers KM, Lind L, Ahlstrom H, Bjerner T, Ebeling BC, Larsson A, *et al.* Prevalence and pathophysiological mechanisms of elevated cardiac troponin I levels in a population-based sample of elderly subjects. Eur Heart J 2008 Sep; 29(18): 2252-58.

8. Venge P, Arnlov J, Zethelius B. Seemingly healthy 71-year-old men with minor elevations of cardiac troponin I and at risk of premature death in CVD have elevated levels of NT-proBNP: report from the ULSAM study. Scand J Clin Lab Invest 2009; 69(3): 418-24.